The Healthy Thyroid

Introduction

The thyroid gland makes thyroid hormone. Thyroid hormone provides the spark that ignites all cells into action. Without it, nothing goes. With too much, every cell "goes too much." By the end of the lesson, this will make intuitive sense, even if you don't know exactly what it means from the start. We start this lesson with a little warmup, gross anatomy and histology of the thyroid. Then we move into a complex discussion of physiology. Thyroid hormone synthesis, thyroid hormone release, and thyroid hormone intracellular mechanisms are very complex, and some of the details are not well understood. We close with thyroid regulation, which thankfully follows classic negative feedback, making the interpretation of thyroid function studies easy and predictable. No tricks with the thyroid axis.

Gross Anatomy and Embryology of the Thyroid

The thyroid gland is located in the anterior neck, adjacent to the larynx and trachea. The bulk of the thyroid is in the two **lateral lobes** connected by a slender **isthmus**. The isthmus crosses in front of the **second and third** cartilaginous rings of the trachea. A remnant of its passage from the mouth, a **pyramidal lobe,** extends up from the isthmus. The entire organ is surrounded by a thin **capsule.** The thyroid is perfused by the **superior thyroid arteries** arising from the **internal carotid** and the **inferior thyroid arteries**, arising from the **subclavian**. It isn't just because the thyroid happens to be at the center of major bifurcations that it ends up with blood from so many arteries. As we will see, the thyroid maintains the spark that all cells require for function. It gets all that blood because of its importance. The thyroid is drained by superior, middle, and inferior veins.

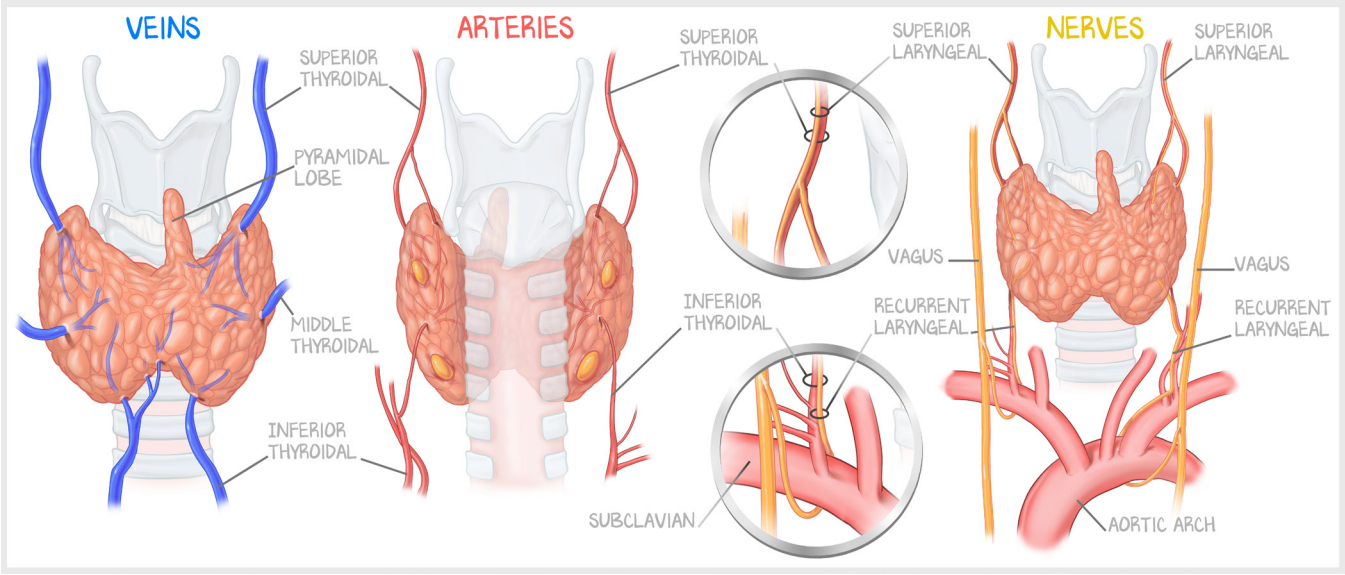

Figure 1.1: Thyroid Anatomy
The thyroid is an anterior neck structure with two lateral lobes connected by an isthmus. Many patients have an additional functional pyramidal lobe (a remnant of the thyroglossal duct) attached to the superior isthmus. There are three sets of veins: superior, middle, and inferior. There are two sets of arteries: superior and inferior. The superior thyroid arteries travel with the superior laryngeal nerve. Damage to the superior laryngeal nerve results in hoarseness. The inferior thyroid arteries travel with the recurrent laryngeal nerve. Damage to the recurrent laryngeal nerve results in the inability to reach a high pitch. In the posterior of the thyroid glands rest the parathyroid glands. If not cautious, they may be removed during thyroidectomy.

A few nearby structures are of critical importance to thyroid surgery but don't participate in the normal function of the thyroid. The **parathyroid glands** sit in the posterior of the thyroid gland, nestled in the connective tissue of the thyroid. There are four of them. During removal of the thyroid, one must be certain not to remove the parathyroid glands as well. The **laryngeal nerves**, the branches of the vagus that innervate all the laryngeal muscles (except the cricothyroid), can be injured when resecting the thyroid because they are near the arteries that feed the thyroid. Anatomic variants exist, but the fact is that the **recurrent laryngeal nerve** (the one that runs under the subclavian and back up into the larynx) crosses or follows the **inferior thyroid arteries**. The **superior laryngeal nerve** (the one that runs from the carotid bifurcation down into the larynx) follows the path of the **superior thyroid artery**.

The thyroid begins development around **week 4 gestational age** from a thickening of the floor of the primitive pharynx. It is an **endoderm-derived organ**. The invagination extends down to its location in the neck through the **thyroglossal duct**. That thyroglossal duct is supposed to involute, severing the connection between the floor of the tongue and the thyroid in the neck. The pyramidal lobe is a product of the thyroglossal duct. The lobes begin to proliferate. Around week 9, endodermal cells differentiate into follicular cells, the cells that line follicles. By week 14, there are well-developed follicles. The disorders of thyroid migration are discussed later in this Thyroid island (Thyroid #3: *The Unhealthy Thyroid—Structural Disorders*).

Histology

A **thyroid follicle** is the smallest functional unit of the thyroid gland. A thyroid follicle is a spherical structure lined with **simple cuboidal epithelium**; the cells of the epithelium are named **follicular cells**. The "outside" of each sphere is the basement membrane of the epithelium, whereas the vast majority of volume within the follicle is **colloid**, a proteinaceous fluid secreted by the epithelium. The follicular cells are oriented such that their **apical domain** is **in the colloid,** and the basal domain projects outwardly towards the edge of the sphere. The basal domain sits on a **basement membrane** that is **shared with the endothelial cells** of the blood vessels that travel between the follicles. It is a proper secretory epithelium with a zona occludens and zona adherens at the apical surface between all cells and cilia to enhance both the secretion into and reabsorption from the colloid. There is an overall polarity to the organelles as well, with the nucleus usually near the basement membrane. As discussed in the next section, the main protein made by the follicular cell is secreted into the colloid, so the RER is usually quite apical. The follicular cell must endocytose colloid and process it in the Golgi or lysosomes before releasing thyroid hormone, so the Golgi is located more centrally, and lysosomes are often abundant.

The gland is made of many follicles, each a malleable sphere of colloid surrounded by a simple epithelium. The follicles are not in any particular arrangement and may appear haphazardly smooshed together. Any one histology section will show follicles at various heights in their sphere—the smaller pools of colloid have been sectioned near the top of the sphere, with wider pools of colloid near the sphere's middle. Although these follicles may bump against each other and deform each other's shape modestly, between each follicle is a **fenestrated capillary** whose endothelium shares the basement membrane with the epithelial cells.

In addition to the follicular cells, there are **parafollicular cells**. Sparsely present, they wiggle between the follicular cells. They are on the epithelial side of the basement membrane but **do not touch colloid**. There are so few of them, and they are so hard to see on light microscopy, that this epithelium is still considered simple. Also known as **C cells** because they secrete **calcitonin**, their role in health has not been well elucidated. With the parathyroid gland being a much stronger regulator of calcium, calcitonin, which has a fleeting and minuscule impact on calcium levels, seems to have no purpose in humans. In lower animals, it regulates calcium and bone formation. Medullary thyroid cancer is a malignancy of these cells, as we will discuss later in this module. Once thought to be derived from neural crest cells, they are actually from a second population of **endoderm**, just like the follicular cells.

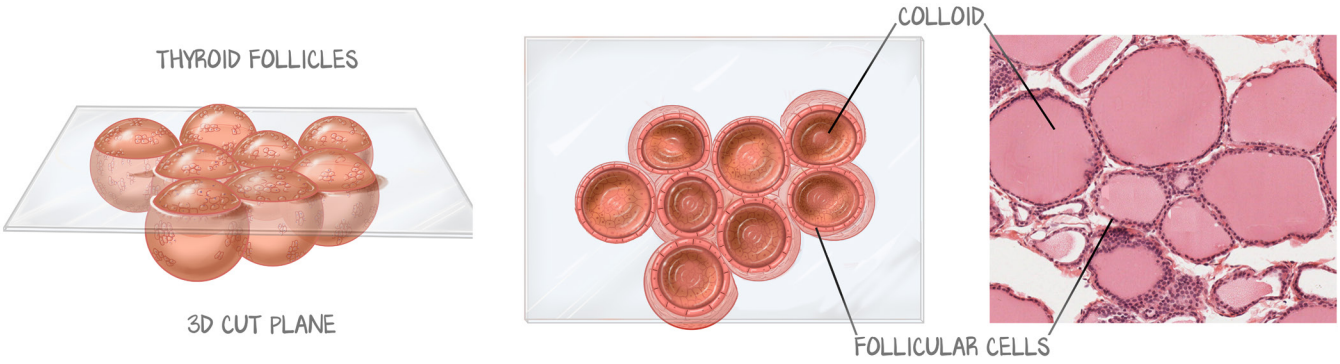

Figure 1.2: Follicles
The thyroid consists of many spheres—follicles—packed closely together. Each sphere is about the same as the others. All are lined with a simple cuboidal epithelium, its basement membrane facing out from the edge of the sphere. The apical domain projects microvilli into the colloid. On histology, on a two-dimensional section, the follicles appear to be of varying sizes. They are not different sizes, but rather the planar section catches different follicles at different levels.

The C cells seem to represent an evolutionary progression. C cells are derived from endoderm that penetrates the follicles of the thyroid. Calcitonin directs osteoclasts to stop clearing bone. The parathyroid glands are derived from endoderm and nestle into the posterior of the thyroid. Parathyroid hormone has master control over calcium—including the activity of osteoblasts and osteoclasts, the renal tubules, and vitamin D. It may be a coincidence, but the parathyroid glands seem to be a more robust version of the C cells that follow a similar course and purpose.

Physiology of Thyroid Hormone Synthesis

We use the phrase **thyroid hormone** when speaking generally of T_3 and T_4 function, whereas **T_3** and **T_4** will be used only when discussing something specific to those individual molecules. Because T_4 is converted to T_3 in the peripheral tissue, and T_3 has a major impact on cell function, thyroid hormone is thyroid hormone for all intents and purposes. But when we need to separate them expressly, we will name them individually. T_3 and T_4 are iodinated tyrosine residues. Out story begins, then, with iodide.

Iodide (I^-) comes into the follicular cell from the bloodstream through a **sodium-iodide cotransporter** (the Na^+/I^- symporter, abbreviated NIS), sodium going down its concentration gradient, bringing iodide up its concentration gradient. There is no mechanism for iodide to leave the basolateral membrane, and thus iodide is now trapped in the cytoplasm. The iodide must get from the basement membrane to the apical surface in the cytoplasm. Iodide is then pumped into the colloid using a chloride-iodide antiporter called **pendrin**. Immediately upon entering the colloid, the iodide is **oxidized to iodine** (I^0 the elemental form, not I_2 iodine gas) by the enzyme **thyroid peroxidase**. Thyroid peroxidase is a transmembrane protein in the apical membrane with its catalytic domain in the colloid. As soon as the iodide enters the colloid, that catalytic domain oxidizes the iodide to iodine (I^0 not I_2) and also sticks that iodine onto a tyrosine residue on thyroglobulin, a process called **organification**. To the iodine, the process is organification. To the thyroglobulin, the process is iodination. There is more to the story, but let's pause the iodide story for a moment and back up to the RER to tell the story of how thyroglobulin and thyroid peroxidase got here.

Thyroglobulin is synthesized in the RER, packaged in the Golgi, and dispatched to the apical surface, where it undergoes exocytosis into the colloid. Thyroglobulin is a **massive protein**, and it accounts for approximately half of the protein content of the thyroid gland. It has relatively few tyrosines (~100 per molecule of Tg), and only a small subset of those will get iodinated. Thyroglobulin is synthesized within the membrane because it is destined for exocytosis into the colloid. **Thyroid peroxidase** is synthesized as an integral protein. The vesicle from which thyroglobulin is released by plasma membrane fusion also contains thyroid peroxidase in its plasma membrane.

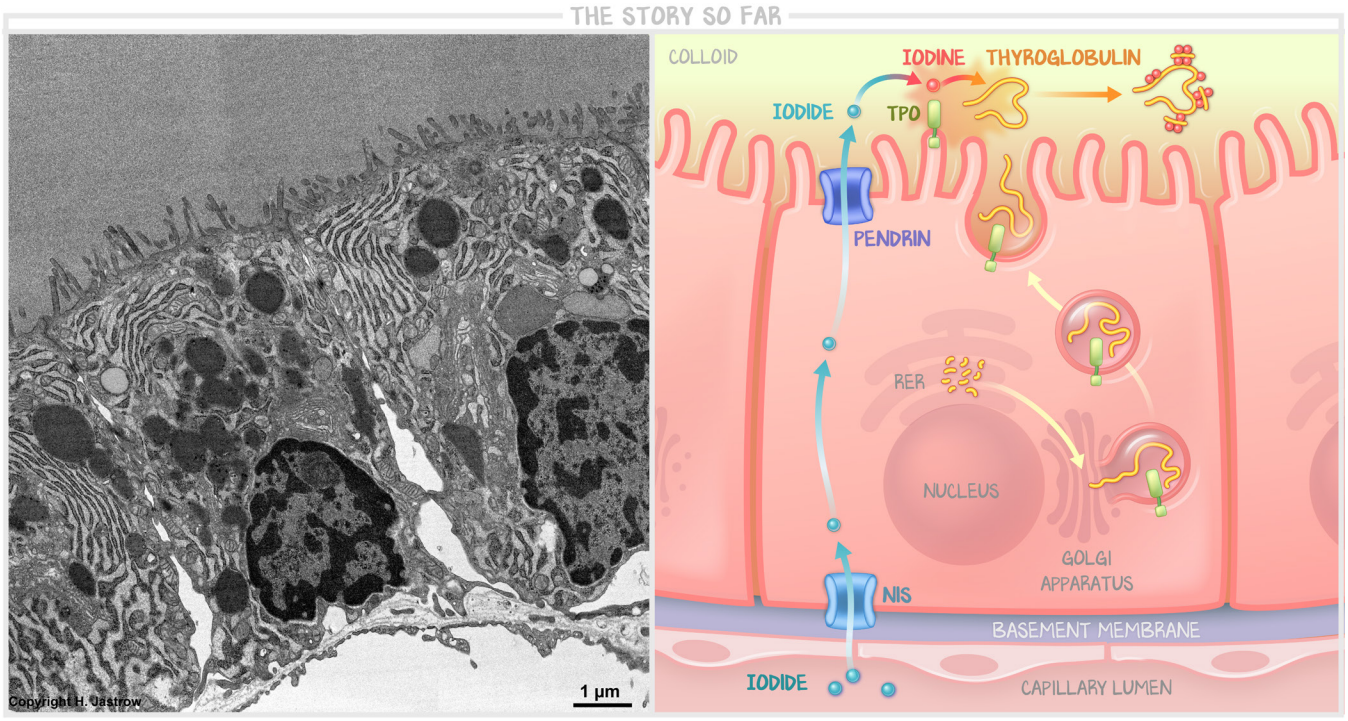

Figure 1.3: The Story So Far
An electron micrograph demonstrates the orientation of the illustration: the basement membrane and the capillary at the bottom, nucleus near the basal domain, and microvilli in the apical domain. The cell synthesizes the proteins thyroid peroxidase (TPO) and thyroglobulin and packages them in vesicles. Thyroglobulin is destined for exocytosis, so it is packaged within the vesicle. TPO is destined to be in the apical membrane, so it is synthesized as a transmembrane protein. As the vesicle fuses with the apical domain, thyroglobulin is exocytosed into the colloid, and TPO is positioned in the plasma membrane. At the same time, iodide enters through the NIS on the basolateral membrane and is pumped out of the apical membrane by pendrin. As iodide enters the colloid, TPO both oxidizes iodide to iodine and couples iodine to tyrosine residues on thyroglobulin.

As the secretory vesicles fuse with the apical membrane, the catalytic domain faces the follicular lumen and catalyzes the oxidation of iodide to iodine. As it does, thyroglobulin diffuses out of the vesicle into the colloid, where thyroid peroxidase iodinates the tyrosine residues. Some tyrosine residues get one iodination (**mono-iodo-tyrosine**), and some get two (**di-iodo-tyrosine**). Thyroid peroxidase, in the presence of H_2O_2, catalyzes the **coupling** of two iodinated tyrosyl residues within the Tg molecule. This forms a single thyroid hormone molecule as well as a remnant dehydroalanine. Both remain as part of the primary structure of the iodinated Tg until it is later degraded inside the follicular cell. T_4 is made by the coupling of two di-iodo-tyrosines, T_3 by the coupling of a mono onto a di, and reverse T_3 by the coupling of a di onto a mono.

That means that thyroid peroxidase is an integral membrane protein with its active site exposed to the colloid. It catalyzes the reaction of **oxidation** (I^- to I^0), **organification** (one or two I^0 on tyrosine), and the **coupling** of iodinated tyrosines together to make thyroid hormone.

Thyroglobulin storage. The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After the synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine (T_4) molecules and a few triiodothyronine (T_3) molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2–3 months. Therefore, when the synthesis of thyroid hormone ceases, the physiological effects of deficiency are not observed for several months.

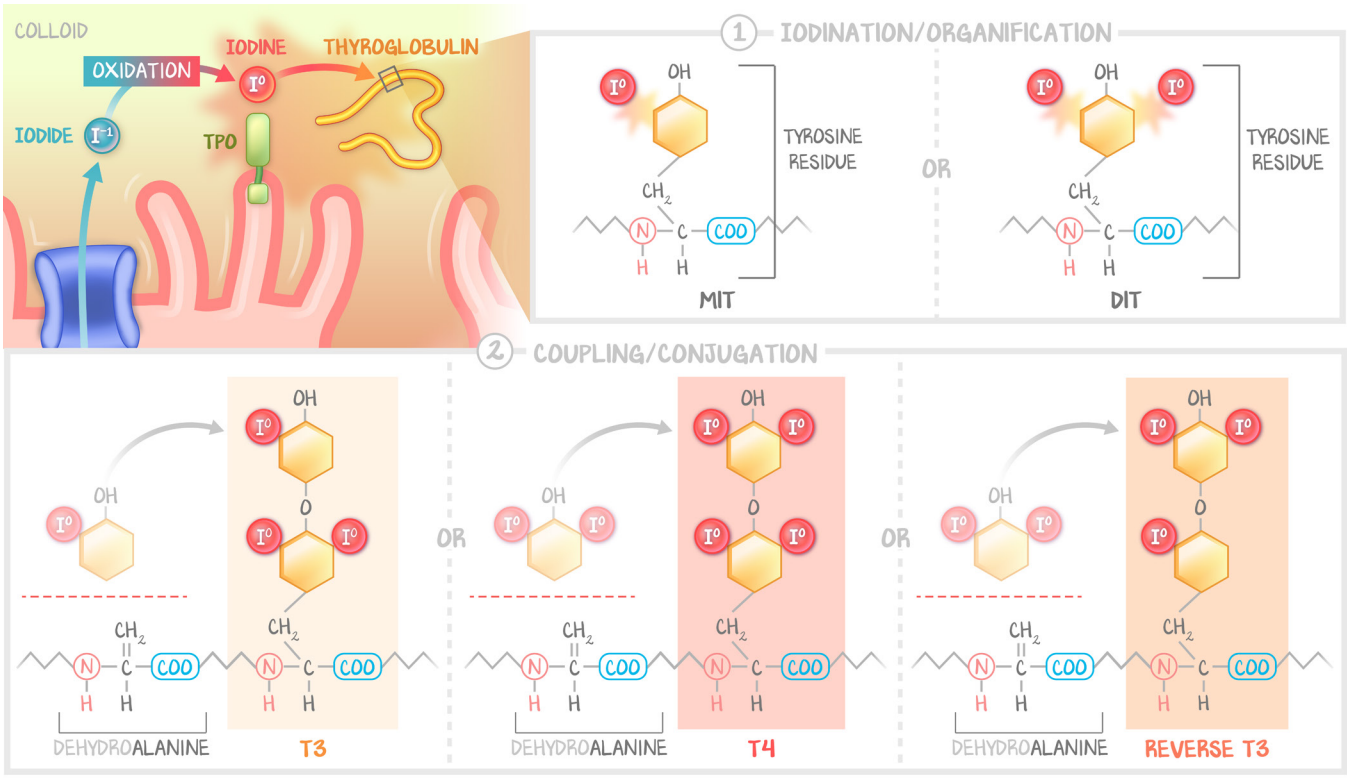

Figure 1.4: Iodination and Conjugation of Tyrosine
Thyroglobulin is an immensely long amino acid chain. Some of those amino acids are tyrosine. Any one tyrosine can be iodinated once or twice, forming mono-iodo-tyrosine (MIT) or di-iodo-tyrosine (DIT). To tyrosine, the process is iodination (gaining iodine). To iodine, the process is organification (added to a carbon-based molecule). Those MITs and DITs remain part of the amino acid chain. After iodination, thyroid peroxidase performs conjugation. Conjugation clips the tyrosine amino acid at the first connecting carbon, thereby maintaining the continuous chain of molecules, amine to carboxyl. Therefore, what gets clipped off isn't a full tyrosine molecule, but a tyrosine molecule missing the two carbons at the end. That leaves behind an alanine in the amino acid chain of thyroglobulin. The partial tyrosine that is removed is then attached to the end of a still wholly intact tyrosine that is still part of the amino acid chain of thyroglobulin. This new combination of tyrosine-with-iodine and the almost-tyrosine-with-iodine is thyroid hormone. When an MIT is coupled to a DIT, it is T_3. When a DIT is coupled to a DIT, it is T_4. When a DIT is coupled to an MIT, it is reverse T_3.

Physiology of Thyroid Hormone Release

Under the influence of thyroid-stimulating hormone (TSH), the follicular cells reabsorb colloid and release thyroid hormone. This, much like thyroid hormone movement across membranes, is not well elucidated. Some elements of that reabsorption and release are, however. Use Figure 1.5 to follow along with the text.

Pinocytosis definitely happens. The unregulated, receptor-independent process of blebbing small amounts of plasma membrane with small amounts of colloid happens all the time. All cells with a plasma membrane do this all the time (General Physiology #1: *Plasma Membranes*). It is a product of membrane fluidity. The pinocytic vesicle is recycled by the Golgi and not dispatched to a lysosome or to the basal domain of the cell. Pinocytosis plays only a small part, if any, in the release of active hormone.

Fusion with a lysosome is required to release active hormone. TSH binding to its receptor on follicular cells induces the endocytosis of colloid (nebulously described this way because the mechanism is not clear). The active endocytosis is characterized by large endosomes at the apical surface, called colloidal reabsorption droplets. These colloid reabsorption droplets are trafficked towards the basal domain of the cell and are fused with a lysosome (General Physiology #3: *Membrane-Bound Organelles*)

before reaching the basal domain of the cell. Within the lysosome, **proteases degrade thyroglobulin**, breaking the amine bonds between neighboring amino acids. All amino acids are separated from one another. This results in several iodinated tyrosines that were never coupled (MIT, DIT), and the iodinated and coupled T_3 and T_4. All amino acids (i.e., not T_3 or T_4) are recycled and sent back to the Golgi. **5'-deiodinase** removes the iodine from MIT and DIT, resulting in many amino acids and some iodine that can make more thyroglobulin. Again with a poorly elucidated mechanism, T_3 and T_4 are released from the basolateral domain into the bloodstream.

Megalin drives the transepithelial pathway. When there is excess TSH stimulation, a very well-elucidated mechanism of clathrin-mediated receptor-induced endocytosis occurs. The receptor **megalin** is activated by thyroglobulin. This induces the endocytosis of colloid and marks the endocytic vesicle (the endosome) to **stay clear of lysosomes**. Instead, the vesicle is trafficked to the basal domain, where the vesicle fuses with the plasma membrane, releasing thyroglobulin into the bloodstream. The whole protein, with the T_3s, T_4s, MITs, and DITs still attached, is released **without lysosomal processing**. This release of thyroglobulin ensures only that the T_3 and T_4 that had been conjugated on that thyroglobulin molecule will never be released as active hormone into the bloodstream. This is a fail-safe mechanism that prevents excess thyroid hormone from being released. The more TSH activity, the more thyroid hormone is released AND the more megalin activity there is, so the more thyroglobulin is released.

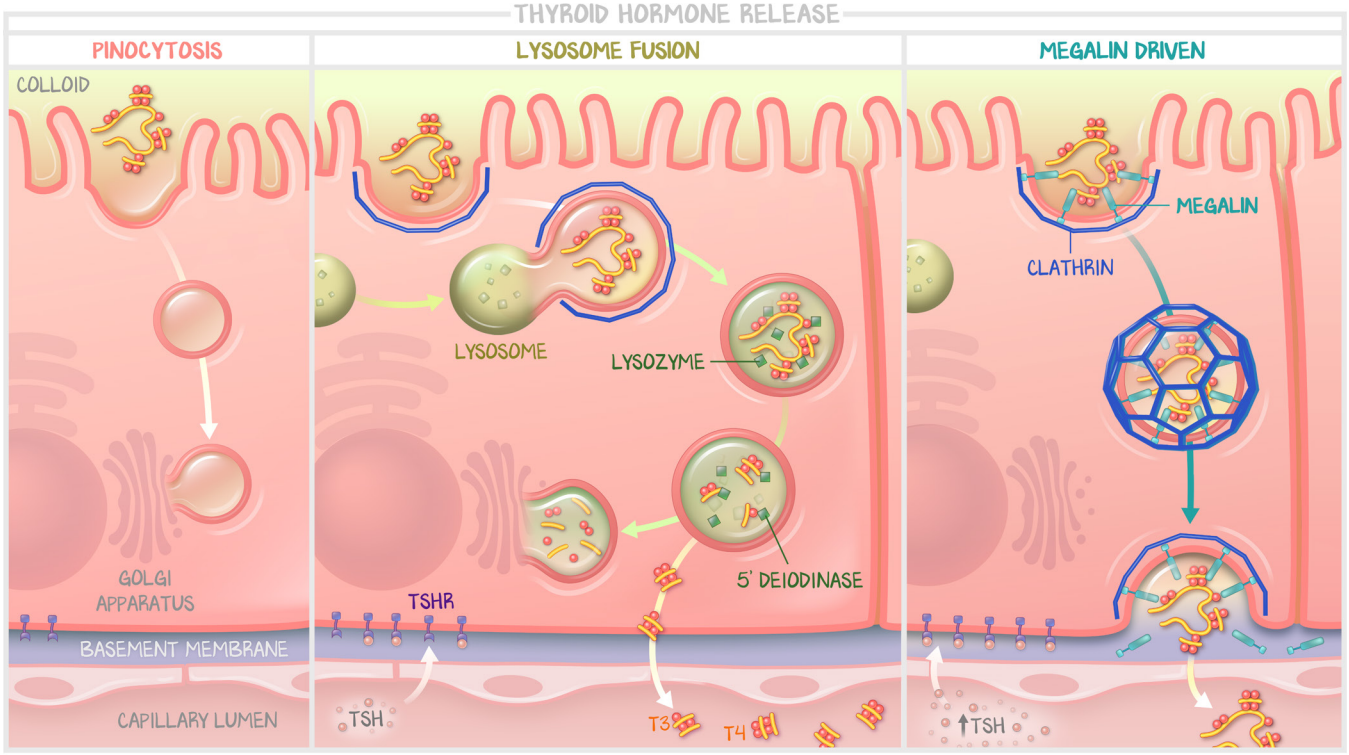

Figure 1.5: Colloid Reabsorption and Thyroid Hormone Release
A visual representation of the preceding paragraphs. Pinocytosis is not part of thyroid hormone reabsorption and release. The megalin pathway is clathrin-mediated endocytosis that bypasses lysosomes and wastes thyroglobulin. An unknown mechanism of endocytosis results in the endosome fusing with a lysosome, degrading thyroglobulin to its constituent parts, deiodinating MIT and DIT, and somehow releasing T_3 and T_4 into the bloodstream without being degraded.

Thyroid Hormone in Circulation

In the circulation, both T_4 and T_3 are tightly bound to plasma proteins. **Thyroid-binding globulin** (TBG), **albumin**, and **transthyretin** (TTR) account for most of this binding. The affinity of these binding proteins is sufficiently high that, for T_4, > 99.98% of the hormone circulates tightly bound to protein. T_3 is bound only slightly less: ~99.5% is protein-bound. Because the free or unbound hormone in the circulation is responsible for the actions of the thyroid hormones on their target tissues, the large amount of bound hormone has considerably confounded our ability to use simple measurements of the total amount of either T_4 or T_3 in the plasma as a reliable index of the adequacy of thyroid hormone secretion. In routine laboratory testing, we use the TSH and total T_4 levels to assess a patient's thyroid status. However, the total T_4 levels may be misleading. When labs are incongruent, **free T_4** can be ordered instead. This is a more expensive test, so it is used only when the total T_4 does not match the TSH or the patient's condition.

We'll discuss the clinical significance of this in the next lesson (Thyroid #2: *The Unhealthy Thyroid—Functional Disorders*) when we talk about laboratory interpretation.

Thyroid Hormone in Target Tissues

To master thyroid hormone function, we must consider three microenvironments: calorie metabolism, cellular respiration, and the whole-body human this is going on in. We discuss the outcome of the thyroid hormone activity and then discuss the intracellular mechanisms that make this happen.

Calorie metabolism. Thyroid hormone shifts the body into the glucagon-dominant state. Regardless of the blood sugar or the activity of the pancreas, thyroid hormone's net effect on calorie metabolism is **lipolysis** in **adipose** and **amino acid catabolism** in **skeletal muscle**. These both provide the liver with the nutrients it needs to make its own ATP, providing the energy required to perform **gluconeogenesis**. The organs of metabolism are turned towards a make-energy-for-others state.

Cellular respiration. In skeletal muscle and adipose, thyroid hormone **stimulates amino acid anabolism** and **lipogenesis**. Yes, thyroid hormone does both—liberates lipids for fatty acid oxidation by the liver and induces the formation of new lipids from fatty acids in adipose cells. Yes, thyroid hormone does both—liberates amino acids from skeletal muscle and stimulates the formation of new amino acids. Thyroid hormone stimulates energy consumption. By inducing systemic protein synthesis and degradation, as well as lipogenesis and lipolysis, thyroid hormone promotes **futile cycles** that contribute significantly to increased O_2 consumption. This generates **heat**. But it does something else to all cells other than those in the liver, skeletal muscle, and adipose. Because thyroid hormone does not oppose the activity of insulin, as the thyroid-induced hepatic gluconeogenesis causes rising blood glucose, the pancreas responds with increased insulin expression. In hyperthyroidism, there is no hyperglycemia. Instead, thyroid hormone ensures that the liver makes sufficient energy to be consumed by all other cells. Thyroid hormone **increases all cells' metabolic rate**, getting all cells to do what they do. Part of that is simply burning energy by **increasing the transcription of Na^+/K^+-ATPases**—more futile ATP usage to generate energy, thereby demanding more glycolysis, citric acid cycle, electron transport chain. To do this, **mitochondria** multiply as well. The other part of that is doing what the cell is supposed to do. Too much thyroid hormone is wasteful. Too little thyroid hormone and the cells don't function at all.

The human. When the body is running well, when the metabolic rate is appropriate and the person is in homeostasis, most of the thyroid hormone is bound to proteins circulating in the plasma. Everything is working. Everything is working because there is the right amount of spark. You don't feel what that spark does because it is kept at the right level. So to understand what "alterations in the metabolic rate" of other cells means, we must turn to disease. When there is **too much thyroid hormone** (hyperthyroidism), all of the actions of all the cells increase. The heart beats harder and faster (**tachycardia/AFib**), GI motility increases (**diarrhea**), the amount of heat generated increases (**heat intolerance**), and energy is burned

(**weight loss**) despite an **increased appetite**. The skin becomes warm and flush. The nervous system is upregulated, presenting with tremor, hyperactivity, inability to concentrate, wakefulness, emotional lability, and **increased deep tendon reflexes**. Finally, there is increased osteoclast activity, leading to **bone resorption**, hypercalcemia, and osteoporosis if allowed to continue long-term. Conversely, the opposite is true with too little thyroid hormone. Bradycardia, constipation, cold intolerance, weight gain, decreased appetite. **Myxedema** is the word given to the development of hypothyroidism that is not congenital, acquired as an older child or adult (so not cretinism, below). Myxedema is marked by a slowing of physical and mental activity. The initial symptoms include generalized fatigue, apathy, and mental sluggishness, which may mimic depression. Speech and intellectual functions are slowed. Patients with myxedema are listless, cold intolerant, and frequently overweight. In the extreme, the patient progresses into a coma. Even the smooth muscles of blood vessels don't cooperate, resulting in hypotension (vasodilation) and edema (fluid leaking). Every organ is affected.

Thyroid in normal growth. Again, this paragraph illustrates the necessity for the "spark" in all cells by describing what happens when it isn't there. **Childhood hypothyroidism** (not maternal hypothyroidism through pregnancy, but the development of hypothyroidism in a healthy child) is called **cretinism**. Endemic cretinism has been characterized by licensing exams as children growing up with iodine-poor diets. The correction of iodine deficiency (by putting it everywhere, such as in table salt) has essentially eliminated endemic cretinism in developed nations. Cretinism is characterized by profound mental retardation, short stature, delayed motor development, coarse hair, and a protuberant abdomen. A child becomes a "simple cretin" (from which the disease gets its name). Specifically, the **mental retardation** that accompanies the syndrome—the brain needs the spark to develop—is irreversible. Unless iodine treatment (or thyroid hormone replacement) is started within the first two weeks of life, mental development never recovers. The longer the duration and the more severe the deficiency, the worse the outcome. Without thyroid hormone, there will invariably be mental retardation (the process) so severe that it will lead to intellectual disability (the diagnosis). In addition, for children with normal thyroid function at birth, the development of hypothyroidism at any time before the fusion of the epiphyses of the long bones leads to **growth retardation**. It does not cause the fusion of the growth plates, but without the spark, the chondrocytes don't proliferate, and so the long bones don't grow. Unlike mental development, much of the loss in height that occurs can be recovered after thyroid hormone treatment is begun, a phenomenon called **catch-up growth.** Bones and height catch up, the mental function does not.

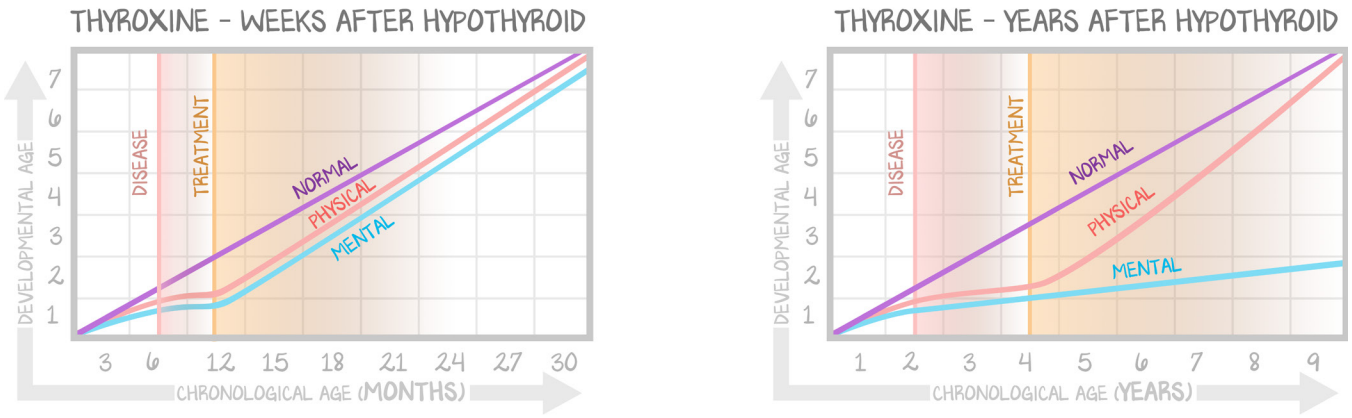

Figure 1.6: Effect of Thyroid Hormone on Growth and Development
The graph shows developmental age—that is, the child's apparent age based on height, bone radiography, and mental function—vs. chronological age. The relationship is a straight line (purple) for a normal child—developmental and chronological age are identical. The two graphs depict the intervention of acquired hypothyroidism (not congenital hypothyroidism known as cretinism). On the left, early intervention with thyroid hormone rescues both physical and mental development. On the right, delayed intervention with thyroid hormone will manage to rescue the patient from growth retardation, but the mental retardation cannot be reversed. The severity of mental retardation may result in intellectual disability or milder intellectual dysfunction, depending on the severity and duration of hypothyroidism.

Intracellular Mechanisms—Lighting the Spark

Despite being so important in literally every cell of every organ, not much is known of the exact mechanisms by which thyroid hormone enters the cell or executes its function. It was once thought that thyroid hormone is like a steroid hormone and can diffuse through plasma membranes. We definitely know that cells have thyroid hormone transporters that bring the molecule into the cytoplasm. It appears to be a polar molecule and so shouldn't be able to diffuse through membranes. And yet, concerning the formation of thyroid hormone from the lysosome, medical science has not elucidated whether there is vesicle fusion with the release of thyroid hormone (not lipophilic), whether there are cytoplasmic pumps, or whether the molecule simply diffuses out of the cell. And likewise, we don't know how thyroid hormone gets into other cells. But we do know what thyroid hormone does once inside.

The **thyroid hormone receptors** (TRs) are **nuclear receptors**. Unlike steroid hormone receptors, there is no chaperone molecule to displace and no translocation from the cytoplasm to the nucleus. Instead, the thyroid hormone receptor has already formed a heterodimer with the **retinoid X receptor (RXR)** at thyroid hormone response elements (TREs) in the DNA in the nucleus. Thyroid hormone enters the nucleus and binds its receptor. After binding with thyroid hormone, the receptor becomes activated and **regulates transcription**. Because they "provide the spark," and are the "go" signal, TREs tend to promote transcription (except in thyrotropes, as discussed next).

Biologically, T_3 is much more important than T_4. The *total* concentration of T_4 in the circulation is ~50 times that of *total* T_3. Nevertheless, T_3 has greater biological activity for three reasons. First, T_4 is bound more tightly to plasma proteins than T_3 is, such that the *free* T_4 and *free* T_3 in the circulation are comparable. Second, the target cell converts T_4 to T_3 using **5'-deiodinase**. That is because, third, the TR in the nucleus has ~10 times greater affinity for T_3 than for T_4. T_4 has a much longer half-life than T_3. Therefore, T_4 acts as a reservoir for T_3.

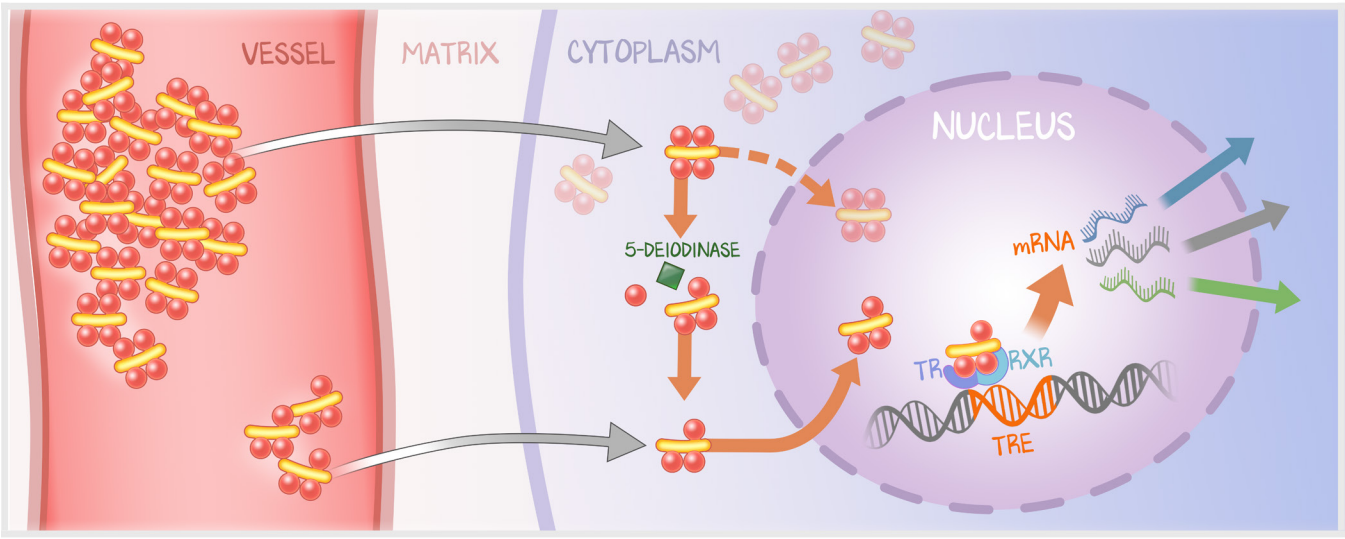

Figure 1.7: Thyroid Hormone Receptor Activation
There is 50 times as much T_4 as T_3 in circulation, which means there is also 50 times as much T_4 as T_3 in the cytoplasm. Although T_4 can activate the thyroxine receptor, T_3 does so with a much higher affinity (around 10x). Instead, it appears that T_4 acts more as an intracellular reservoir of T_3, as all cells possess cytoplasmic 5'-deiodinase, converting the T_4 to T_3. Thyroid hormone binds to its receptor, which is already bound to its response elements on the DNA. Together with the retinoic acid receptor, thyroid hormone receptor activation results in gene transcription (the genes transcribed are dependent on which cell type it is, but without thyroid hormone bound to its receptor, the cell does nothing).

Regulation and Receptor Mechanism

TRH is secreted from the hypothalamus. The default hypothalamus signal is to synthesize and release thyrotropin-releasing hormone (TRH). It is controlled through classic negative feedback by the products it ultimately produces—both the anterior pituitary's TSH and the thyroid's thyroid hormone inhibit TRH release. Hypothalamic neurons release TRH into the hypophyseal portal circulation, where it is delivered to the anterior pituitary.

TRH stimulates TSH release. Once TRH reaches the thyrotropes in the anterior pituitary, TRH binds to the TRH receptor, a G protein-coupled receptor, activating the **G_q-DAG/IP_3-Ca^{2+}** pathway. Both arms of this pathway play a role in the thyrotrope. The formation of diacylglycerols (DAGs) stimulates protein kinase C and leads to protein phosphorylation, ultimately **increasing TSH gene transcription**. The simultaneous release of inositol trisphosphate (IP_3) triggers Ca^{2+} release from internal stores, raising the intracellular calcium, resulting in vesicle fusion and **exocytosis of TSH**. The result is an increase in both the synthesis and release of TSH. TSH is a peptide hormone stored in vesicles; those vesicles dock and release TSH into the portal circulation as calcium levels rise.

TSH stimulates thyroid cells. Thyrotropin and thyroid-stimulating hormone are two names for the same molecule. It is a glycosylated hormone, having the same α-subunit as other glycosylated hormones (hCG, FSH, LH) and a unique β-subunit. The **TSH receptor** on the thyroid follicular cells is a G protein-coupled receptor. Like receptors for the other glycoprotein hormones, the TSH receptor acts through the G_s-AC-cAMP-PKA pathway. The rise in intracellular cAMP induces essentially every step of the synthesis, colloid uptake, thyroglobulin processing, and thyroid hormone release.

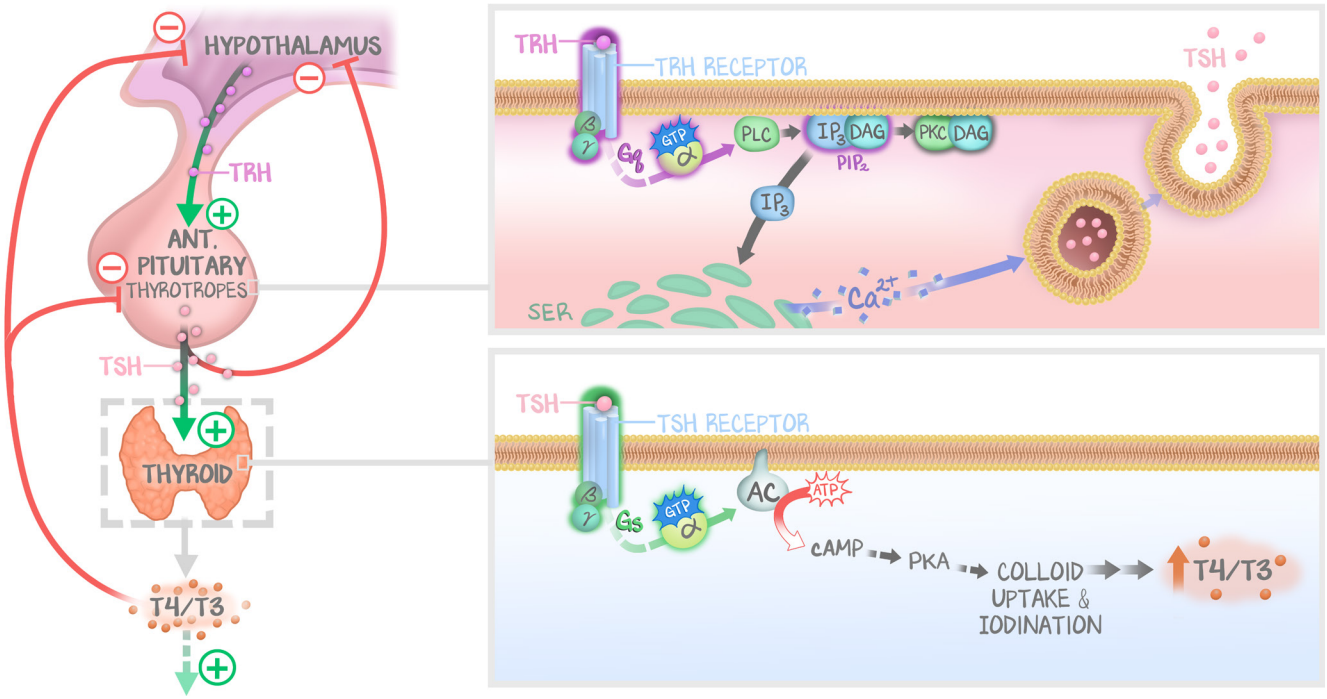

Figure 1.8: Thyroid Axis Regulation
A classic example of a hypothalamic-pituitary axis with positive feedforward down the axis and negative feedback up the axis. In the pituitary, the TRH receptor acts through G_q-IP_3-Ca^{2+}. The calcium release from the smooth endoplasmic reticulum results in vesicle docking and the exocytosis of TSH. In the thyroid, the TSH receptor acts through G_s-AC-cAMP-PKA, resulting not only in colloid uptake for the release of T_4 and T_3, but also an increase in the uptake of iodide from the blood and the synthesis of more thyroglobulin. There is no vesicle waiting to dock, but rather an ocean of colloid waiting to be taken up.

Thyroid hormone inhibits the anterior pituitary. The negative feedback of T_4 and T_3 on TSH release occurs **inside thyrotropes** of the anterior pituitary. T_4 and T_3 can diffuse through the plasma membrane or are brought in by transporters. T_4 deiodinates spontaneously to T_3. T_3 acts inside the cell by two mechanisms—direct and indirect. In the **indirect feedback** pathway, intracellular T_3 **decreases the number of TRH receptors** on the surface of the thyrotrope. As a result, T_3 indirectly inhibits TSH release by reducing the sensitivity of the thyrotropes to TRH. In the direct feedback pathway, intracellular T_3 **inhibits the gene transcription** of both the **α and the β chains of TSH**. Indeed, both the α and β TSH genes have T_3 response elements in their promoter regions. These inhibitory response elements differ from those found in genes positively regulated by T_3 in other tissues (such as the NA^+/K^+-ATPase).

Citations

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